Remarks/Arguments

Claims 10, 19-36, 41 and 42 have been withdrawn from consideration as being drawn to a non-elected invention and species. Claims 1-4, 6, 9, 13, 17 and 18 have been amended. Claims 37, 39 and 40 have been canceled and new claims 43 and 44 have been added. More claims have been canceled than added, therefore no additional claim fees are required.

Claims 1 and 2 are amended to substitute the words "inhibiting" and "inhibits" in place of "regulating" and "regulates", with support for the amendment found in the specification at page 7, line 9-13 and claim 37. Claim 39 has been incorporated into claim 1. Additional support for the amendment may be found on page 20, lines 16-28 and in the paragraph that bridges pages 22 and 23 of the specification. Claims 1 and 2 are now directed to methods utilizing three or more agents non-inclusive of the immunotoxins described in Digan et al. The claims are also amended to correct the antecedent basis of the word "cell-mediated".

Claims 3 and 4 are amended by incorporating claim 39. Additional support for the amendment may be found on page 20, lines 16-28 and in the paragraph that bridges pages 22 and 23 of the specification. Claims 3 and 4 are now directed to methods utilizing three or more agents non inclusive of the immunotoxins described in Digan et al. Both claims 3 and 4 have been amended to include "by" clarifying that the first, second and third agents treat the immune system disease by blocking the CD28/CTLA4/B7-mediated signal, the CD40/CD154-mediated signal and the adhesion molecule-mediated signal respectively. Support for this amendment may be found throughout out the specification, specifically on page 15, lines 4-13. Claim 3 is also amended to correct the antecedent basis of the phrase "immune system disease".

Claim 6 has been amended to remove the ATCC listing for an anti-CD28 monoclonal antibody, designated ATCC 11944. There is no web page on the ATCC site for HB-11944; however the ATCC 11944 is listed in the comments section of ATCC HB-12352.

Claim 9 has been amended to correct the antecedent basis, for dependent claim 11, of the word "antibody" for anti-ICAM-1, anti- α -actinin, anti-CD18 and anti-CD11 antibodies. Support may be found on page 8, lines 24-30.

Claim 11 has been amended to remove the "(e.g.)" thereby clearly listing the claimed immune system diseases.

Claims 17 and 18 are amended by incorporating claim 39. Additional support for the amendment may be found on page 20, lines 16-28 and in the paragraph that bridges pages 22 and 23 of the specification. Claims 17 and 18 are now directed to methods utilizing three or more agents non inclusive of the immunotoxins described in Digan et al.

Support for new claim 43 may be found on page 15, lines 21-23 of the specification, and original claims 4, 5 and 6. New claim 43 is a combination of original claims 4, 5 and 6 with the first agent that blocks a CD28/CTLA4/B7 mediated signal limited to L104EA29Ylg. No new matter has been added.

New claim 44 is supported in the specification as originally filed on page 20, lines 16-28 and in the paragraph that bridges pages 22 and 23 of the specification and original claim 39. No new matter has been added.

Applicants' claimed invention is directed to the use of the following three agents to inhibit a cell mediated immune response, treat an immune system disease or inhibit transplant rejections: a first agent that blocks a CD28/CTLA4/B7-mediated signal e.g., soluble CTLA4, L104EA29Ylg, 2) a second agent that blocks a CD40/CD154-mediated signal e.g., anti CD 154 antibody, and 3) a third agent that blocks an adhesion molecule-mediated interaction e.g., anti-LFA-1 antibody. The three agents described above may optionally be administered in conjunction with one or more immunosuppressive/immunomodulatory or anti-inflammatory agents.

35 USC 112 Rejections

Claims 1, 2, 5-9, 11-17 and 38-40 are rejected under 35 USC 112, second paragraph, as being indefinite in its recitation of "regulating". While not agreeing with the rejection, the following amendments are being made to advance the prosecution of this application. As suggested by the Examiner, the claims have been amended to recite a clear and definite endpoint by substituting the words "inhibiting" and "inhibits" in place of "regulating" and "regulates". Support for this amendment may be found on page 7, line 9-13 and claim 37.

Claim 40 was also rejected under 35 USC 112, second paragraph, as being indefinite in its use of the trade names "etanercept" and "anakinra". While not agreeing with the rejection, the following amendments are being made to advance the prosecution of this application. Claim 40 has been canceled thereby rendering the rejection moot. In view of the amendments, the Applicants respectfully request that he rejection to claims 1, 2, 5-9, 11-17 and 38-40 be withdrawn.

35 USC 102(e) Rejection

Claims 1-7, 9, 12-18 and 37-40 are rejected under 35 USC 102(e) as being anticipated by Digan et al. (US 2002/014200 A1). Digan teaches the use of an isolated recombinant immunotoxin that consists of a CD3-binding domain and a Pseudomonas exotoxin A component to effect T-cell depletion in order to treat or prevent T-cell mediated diseases or conditions of the immune system. The immunotoxins may be utilized in methods carried out *in vivo*, in order to systemically reduce populations of T cells in a patient. The immunotoxin may be administered either alone or in

combination with other pharmaceutical agents effective in treating acute or chronic transplant rejection (paragraph 0198).

While not agreeing with the rejection, the following amendments are being made to advance the prosecution of this application. Independent claims 1, 3, 4, 17 and 18 have been amended by substituting the phrase "consisting of" in place of "comprising" and "by" thereby limiting the claimed method to the use of agents non-inclusive of the immunotoxins described in the Digan reference. In view of the amendments, the Applicants respectfully request that the rejection to claims 1-7, 9, 12-18 and 37-40 be withdrawn.

35 USC 103(a) Rejections

Claims 1-9, 12-18 and 37-40 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560) and Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456). Applicants respectfully disagree.

Blazer et al (WO 95/34320) describes a method for inhibiting a T cell-mediated immune response. This method comprises administering a first agent which inhibits a costimulatory signal in a T cell and a second agent which inhibits adhesion of the T cell (claim 1). The first agent is said to be an agent which inhibits CD28/CTLA4/B7 interactions. The second agent inhibits the interaction of a variety of adhesion molecules, which do not only include anti-LFA-1 antibody (claim 14) but alternatively anti-gp39 (claim 16). Accordingly, Blazer teaches to combine an agent that blocks the CD28/CTLA4/B7 pathway (such as CTLA4Ig) with <u>either</u> anti-LFA-1 antibody <u>or</u> anti-gp39 antibody resulting in a double pathway therapy.

Larsen et al (US 5,916,560) describes the combination of an agent that blocks the CD28/CTLA4/B7 pathway with and an agent that blocks the gp39/DC40 pathway (double therapy). It is an object of Larsen to discontinue mono- therapies and replace with said two agents (page 7, three paragraphs before the SUMMARY OF THE INVENTION, page 15 in the ADVANTAGES OF THE INVENTION)).

Strom et al.describes the basic principles of immunosuppressive therapy in organ transplantation including the use of different agents, each directed at a different molecular target within the allograft response. Strom lists in Table 36.1(on page 454) agents typically utilized in the standard of therapy for organ transplantation. The list does not include the agents of the claimed invention.

Thus, if Blazer is considered in view of Larsen and the basic principles set forth in Strom et al, at best, the skilled person would consider the use of the standard of therapy agents described by Strom in Table 36.1 in combination with the double therapy pathway described in Blazer <u>or</u> Larsen.

There would be no motivation to combine an agent that blocks the CD28/CTLA4/B7 pathway with and an agent that blocks the gp39/DC40 pathway and an agent that inhibits adhesion of the T cell, with or without the standard of therapy immunosuppressants of Strom especially since Blazer teaches the use of either anti-LFA-1 antibody or anti-gp39 antibody.

In view of the lack of evidence showing the claimed invention is obvious in view of the cited references, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 12-18 and 37-40, under 35 USC 103(a).

Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456) and known availability of the deposited material producing the known immunosuppresives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies. Applicants respectfully disagree.

Since Blazer et al., in view of Larsen et al. and Strom et al. do not render obvious the claimed methods for the reasons discussed above, the fact that reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without the standard of practice agents described by Strom.

Accordingly, the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 6, 8 and 11, under 35 USC 103(a).

Claims 1-9, 11-18 and 37-40 are rejected under 35 USC 103(a) as being unpatentable over Digan et al.(US 2002/014200 A1) in view of Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456) and known availability of the deposited material producing the known immunosuppresives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies. Applicants respectfully disagree.

At best, being aware of the basic principle of multiple therapy described in Strom along with the standard of practice agents listed in Strom and the immunotoxin described in Digan, one skilled in the art would be motivated to add the immunotoxin to a standard multiple therapy described in Strom. The fact that the reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without a standard of practice multiple therapy minus the immunotoxin described in Digan.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 11-18 and 37-40, under 35 USC 103(a).

New claims 43 and 44 are not anticipated or made obvious by the cited art as said art does not teach the use of L104EA29YIg to inhibit a cell mediated immune response, treat an immune system disease or inhibit transplant rejections.

The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment.

The Examiner is invited to contact the undersigned if there are any questions relating to the prosecution of this application.

Respectfully submitted,

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